DIM – indol-3-carbinol – induz diminuição da modulação do cMYC e da família-IAP e promove apoptose linfoma de Burkitt Epstein-Barr vírus positivo, mas, não no EBV negativo.

Indole-3-carbinol induces cMYC and IAP-family downmodulation and promotes apoptosis of Epstein-Barr virus (EBV)-positive but not of EBV-negative Burkitt's lymphoma cell lines.

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Abstract

Indole-3-carbinol (I3C) is a natural product found in broadly consumed plants of the Brassica genus, such as broccoli, cabbage, and cauliflower, which exhibits anti-tumor effects through poorly defined mechanisms. I3C can be orally administered and clinical trials have demonstrated that I3C and derivatives are safe in humans. In this study we show that I3C efficiently induces apoptosis in cell lines derived from EBV-positive Burkitt's lymphomas (virus latency I/II), while it does not have any cytotoxic activity against EBV-negative Burkitt's lymphomas and immortalized EBV-infected lymphoblastoid cell lines (virus latency III). The effect of I3C in EBV-positive Burkitt's lymphoma is very specific, since only I3C and its C6-methylated derivative, but not other 3-substituted indoles, have an effect on cell viability. I3C treatment caused apoptosis characterized by loss of mitochondria membrane potential and caspase activation. I3C alters the expression of proteins involved in the control of apoptosis and transcription regulation in EBV-positive Burkitt's lymphoma cell lines. Among those, cMYC, cIAP1/2 and XIAP downmodulation at mRNA and protein level precede apoptosis induction, thus suggesting a role in I3C cytotoxicity. We also showed that I3C and, more particularly, its condensation dimer 3,3'-diindolylmethane (DIM) prolonged survival and reduced tumor burden of mice xenotransplanted with EBV-positive Burkitt's lymphoma Daudi cells. In summary these results, together with previous reports from clinical trials indicating the lack of toxicity in humans of I3C and derivatives, support the use of these compounds as a new therapeutic approach for treating patients with endemic (EBV-positive) Burkitt's lymphoma.

KEYWORDS:

(6-Methyl-1H-indol-3-yl)methanol (PubChem CID 22062103); 3,3′-Diindolylmethane; 3,3′-Diindolylmethane (PubChem CID 3071); Burkitt's lymphoma; Epstein–Barr virus; Indole-3-carbinol; Indole-3-carbinol (PubChem CID 3712); XIAP; cIAP; cMYC

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